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Transcranial Magnetic Stimulation (TMS) in a 15 year old patient with autism and co-morbid depression

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Dear Sir

Depression is a common co-occurring disorder in patients with autism, with prevalence rates from 1.5% to 10% for major depressive episodes.[1] Transcranial magnetic stimulation is a non-invasive neuromodulation technique that uses pulsating magnetic fields to depolarize cortical neurons. High frequency (≥ 5 Hz) TMS can induce excitatory responses and low frequency (≤ 1 Hz) induces inhibitory responses[2]. TMS has been proposed as antidepressant treatment in adolescents[3] and in patients with autism to improve executive functioning.[4] We present the case of an adolescent with autistic disorder and comorbid depression treated with TMS to illustrate this potential application. Patient's parents (guardians) provided permission for treatment and to use protected health information.

This is a 15 year old male with DSM-IV autistic disorder diagnosis. He was diagnosed at age 5 using the Autism Diagnostic Interview-Revised, the Autism Diagnostic Observation Schedule, in addition to expert clinical diagnosis. He lives with his parents and his fraternal twin, also diagnosed with autistic disorder. He attends high school ninth grade with paraprofessional assistance in the classroom. He has a family history of autistic disorder and depression in second degree relatives. His autistic symptoms include limitations in social interactions, difficulties with coping with change, stereotypic movements and behaviors, and limited and stereotypical language use.

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He has a history of depression since early childhood, with depressive episodes that last several days, characterized by lack of motivation, decreased participation in activities, isolation and crying spells. In addition he exhibited irritability and long-standing extreme sensitivity to negative emotion expressed by his twin brother. He is prescribed olanzapine/ fluoxetine 6/25 mg, guanfacine 4mg, and clonazepam 0.5 mg three times daily Previous psychotropic treatment has been ineffective or induced side effects. These included sertraline, paroxetine, risperidone and aripiprazole. On initial evaluation his parents reported his mood was down, with decreased motivation, variable energy level, increased appetite, psychomotor slowing, irritability, tearfulness and increased stereotypical phrase repetition. Upon initiation of TMS clonazepam was down-titrated to avoid effects on motor threshold.

To treat depressive symptoms we chose low frequency TMS over the right Dorso-Lateral Prefrontal Cortex (DLPFC). Treatments were administered with a Magpro R30 stimulator (Tonica Electronik A/S, Denmark) using a cool-B65 figure eight coil. The Resting Motor Threshold (RMT) determined by the visualization of movement method was 89%.[2] The DLPFC was localized 6 cm anterior in a parasagittal line to the RMT location. TMS was delivered daily at 90% of the RMT, using 1 Hz, 10 seconds on, and 10 -30 seconds off. Treatment was started at 150 Pulses Per Session (PPS) and increased to 300 PPS by the second week. A total of ten sessions of TMS over the right DLPFC were administered with improvement in mood symptoms.

Subsequently, we applied low frequency TMS over the left DLPFC in an attempt to improve core symptoms of autism, modeling previous studies to improve executive functioning in autism[4]. The left RMT was 80%, and the left DLPFC was identified as 6 cm anterior in a parasagittal line to the RMT location. Stimulation was delivered at 90% of RMT, 1Hz, 10 seconds on, and 10 -15 seconds off. The number of pulses per session was increased from 300 PPS to 600 PPS by the fourth week. Upon completion of 20 sessions, TMS was tapered in six sessions over three weeks. Stimulation was well tolerated and side effects included mild headaches, jaw twitch during stimulation and transient dizziness immediately after treatments.

Improvement in both mood and some autism core features were reported by his parents and his educational team. His mood was described as “perkier”, he seemed more active and his energy improved. He appeared better able to cope with daily stresses and no longer had episodes of tearfulness. Improvements in communication and social interactions were noted. He made better eye contact, greeted people more consistently and was more verbal. In addition, he seemed to be more supportive of the emotions of his parents and his twin brother. The academic tutor noticed he focused better during school-related tasks. On mental status exam by his psychiatrist (author JNC) after completion of TMS treatment, the patient appeared more animated and spontaneously communicative than on any prior visit over the course of his treatment.

In this case we used slow TMS over the right DLPFC to treat depression due to its established antidepressant effects, tolerability and safety (lack of pro-convulsant properties)[2]. A metanalysis by Schutter et al[5]. Indicated that slow right- sided, TMS was more effective than sham and likely equally effective to fast frequency TMS over the left

DLPFC in treating depression. The cumulative effect size for right-sided TMS was 0.63 in this metanalsysis encompassing 252 subjects.[5]

Only few studies have used TMS to treat cognitive and behavioral impairments in autism. Sokhadze et al.[4] applied TMS in children and adolescents with autism to improve executive functioning. They hypothesized that low frequency (inhibitory) TMS may restore the balance between cortical excitation and cortical inhibition and improve long- range cortical connectivity - a potential contributor of brain dysfunction in autism-. They applied TMS at 1 Hz, 150 PPS, sequentially to the left DLPFC then to the right DLPFC once weekly for twelve weeks. They evaluated error monitoring and post- error response correction during a visual task pre and post- TMS, demonstrating enhanced behavioral performance with improved error monitoring and correction in the visual attention task in TMS recipients compared to controls.[4]

For this patient we implemented a protocol similar to that described by Sokhadze et al[4] applying TMS to right and left DLPC. Improvements in our patient's behavior, social interactions, ability to cope with change and ability to concentrate in school work were noted.

Main limitations of this report include low treatment parameters and lack of objective measures for depression and executive function. Nonetheless, this is the first report of TMS use in an adolescent with autistic disorder and comorbid depression, demonstrating improvement in mood and adaptive functioning. Randomized control trials are needed to test this potential TMS application.

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